Re: Weighing the Risks and Benefits of Tamoxifen Treatment for Preventing Breast Cancer

In April 1998, the Breast Cancer Prevention Trial (P-1) was halted 14 months early because of a 45% reduction in breast cancer among those patients receiving tamoxifen. At that time, all of the major networks and newspapers made a lead story out of the National Cancer Institute's announcement of this finding. Many of the media reports repeated the investigators' contention that the trial's entry criteria identified women who are potentially eligible for tamoxifen therapy, e.g., all women over the age of 60 years *(1)*.

Now, 1½ years later, the Journal has published a special article entitled "Weighing the Risks and Benefits of Tamoxifen Treatment for Preventing Breast Cancer" *(2)*. Its authors assessed the data from the Breast Cancer Prevention Trial P-1 *(3)* and estimate that the benefits of taking tamoxifen substantially outweigh the risks only for younger high-risk women; conversely, the risks might outweigh the benefits for most black women older than 60 years of age and most white women older than 60 years with a uterus. In other words, tamoxifen therapy is an appropriate consideration for a much smaller subset of high-risk women than was originally thought.

The Journal special article *(2)* states that the risk/benefit assessment grew out of a National Cancer Institute-sponsored workshop held in July 1998. Why did it take so long to get this assessment into print? By contrast, results of the P-1 trial were published by the Journal less than 6 months after the trial ended. Until this assessment was published, it was not known which women are at enough of a high risk to make tamoxifen's potentially fatal side effects worth its potential benefits. Yet as early as October 1998, tamoxifen received U.S. Food and Drug Administration (FDA) approval

for risk reduction which, in turn, allowed its producer, AstraZeneca (Wilmington, DE), to mount an immediate and extensive direct-to-consumer advertising campaign. At the time, we believed that the FDA approval was premature; this assessment only confirms our conviction.

For the first time, an anticancer drug is being marketed to healthy people; more care should have been taken beforehand to estimate who can safely benefit from tamoxifen.

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REFERENCES

(1) Grady D. Breast cancer drug dilemma: who should take it, and when? The New York Times 1998 Apr 14;Sect. Science:1 (col. 4)

(2) Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91:1829–46.

(3) Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998;90:1371–88.

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RESPONSE

Norsigian et al. ask why it took so long to publish the article by Gail et al. *(1)* titled "Weighing the Risks and Benefits of Tamoxifen Treatment for Preventing Breast Cancer," compared with the time it took to publish the data from the Breast Cancer Prevention Trial (P-1) *(2)*. We commend Fisher et al. *(2)* for the speed and elegance of their report. Gail et al., however, faced a much different task from describing a clinical trial. An article that describes a clinical trial has conventional elements *(3)*, many of which can be written before the trial ends, and the methods of analysis are typically prespecified.

Participants at the National Cancer Institute-sponsored workshop in July 1998 gave formal presentations on diverse topics, such as the epidemiology of endometrial cancer and risk perception and communication [*see* the Appendix in Gail et al. *(1)*]. In one subgroup, participants discussed the assessment of the risks and benefits of tamoxifen, while in another subgroup, they discussed risk perception, communication, and counseling. The workshop highlighted important issues and areas of agreement and disagreement, and it yielded key references and contacts for obtaining additional information. It did not, however, produce a consensus on such crucial issues as whether one should summarize risks and benefits in a single index, nor did it resolve critical technical points or provide summary information on which groups of women were likely to benefit from tamoxifen. Although Gail et al. benefitted greatly from the information presented at the workshop, they later collaborated to conduct new research and to prepare a manuscript for which they were solely responsible.

Gail et al. needed to develop a balanced approach to risk/benefit assessment that also identified weaknesses in the method and data sources and presented alternative methods for communicating risk and counseling patients. Some of the most time-consuming aspects of the project were as follows: 1) agreeing on the fundamental risk/benefit approach and on a balanced presentation of the advantages and disadvantages of a summary risk/benefit index; 2) obtaining age- and race-specific data on the incidence of endometrial cancer, stroke, pulmonary embolism, deep vein thrombosis, and fractures in the absence of tamoxifen (published and unpublished sources were explored); 3) developing and implementing statistical methods to assess uncertainty in risk/benefit indices; 4) broadening the scope of the paper to address women who would not have been eligible for the P-1 study and to integrate material on counseling and risk perception with risk/benefit analyses; 5) obtaining and analyzing special data from previous clinical trials to address such issues as the risk of invasive breast cancer in women treated for ductal carcinoma *in situ;* and 6) receiving and integrating suggestions from many sources, including those acknowledged in *(1)*, and peer reviews received from the Journal.

We hope that the broad scope and quality of the special article justify the time and effort required.

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REFERENCES

(1) Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91:1829–46.

(2) Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998;90:1371–88.

(3) Piantadosi S. Clinical trials: a methodologic perspective. New York (NY): John Wiley & Sons; 1997. p. 374–80.

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